Kidney International, Vol. 53 (1998), pp. 799–811

NEPHROLOGY FORUM

Revascularization in atherosclerotic renal artery disease

Principal discussant: STEPHEN C. TEXTOR

Mayo Clinic, Rochester, Minnesota, USA

CASE PRESENTATION

A 69-year-old white male attorney was referred three years ago because of progressive hypertension and declining renal function. He had smoked two packs of cigarettes daily for the past 55 years. Modest hypertension had been successfully treated with a thiazide diuretic for several years. At age 51, an 8 cm abdominal aortic aneurysm was resected. His blood pressure had risen 4 years ago to levels between 170/108 mm Hg and 205/110 mm Hg despite increased medications: pindolol, 5 mg twice daily; prazosin, 5 mg twice daily; and indapamide, 2.5 mg daily. His serum creatinine rose from 0.9 mg/dl at age 52 to 2.0 mg/dl at age 66. He was aware of several episodes of confusion, which had been attributed to lacunar strokes, but he remained able to work and function normally. He had no history of myocardial infarction or angina; an electrocardiogram disclosed left-ventricular hypertrophy. Hyperlipidemia had been treated with lovastatin, cholestyramine, and niacin. His medical history included resection of cancer of the penis and recently detected adenocarcinoma of the prostate, for which radiation therapy had been planned.

Physical examination revealed an alert and functional man. His blood pressure was 205/108 mm Hg; and the pulse was 75 beats/min. The weight was 195 lbs, the height, 69 inches. Ophthalmic examination demonstrated grade II retinopathy. No carotid bruits were heard. Cardiac examination revealed a fourth heart sound. An abdominal scar was present, a result of the abdominal aneurysm surgery. Epigastric and abdominal bruits were detected in every quadrant. Pulses in the lower extremities were diminished. Pitting edema was present at the ankles.

Laboratory data disclosed: hematocrit, 42.8; hemoglobin, 14.9 g/dl; serum creatinine, 2.0 mg/dl; sodium, 140 mEq/liter; potassium, 3.8 mEq/liter; uric acid, 8.4 mg/dl; albumin, 4.2 g/dl; calcium, 9.3 g/dl; PO_4, 3.1 mg/dl; and glucose, 122 mg/dl. Total cholesterol was 180 mg/dl; triglycerides, 122 mg/dl; HDL, 38 mg/dl. Urinalysis disclosed 1+ proteinuria. A chest radiograph demonstrated an elevated right hemidiaphram, scattered fibrosis, and a tortuous aorta. An electrocardiogram showed left-ventricular hypertrophy with strain pattern and was unchanged from previous tracings.

A renal angiogram demonstrated single renal arteries bilaterally with high-grade stenoses at their origins (Fig. 1). Severe atheromatous changes were present in the abdominal aorta, as were postoperative changes of a straight graft repair of the infrarenal abdominal aorta. Bilateral common iliac artery aneurysms were found. High-grade stenosis was present at the origin of the celiac artery. Renal-vein renin values were as follows: right, 13.2 ng AI/ml/hr; left, 10.0 ng/AI/ml/hr; and inferior vena cava, 6.7 ng AI/ml/hr.

Over the three years since he was originally seen, the antihypertensive regimen has comprised indapamide, 2.5 mg daily; pindolol, 5 mg twice daily; and hydralazine, 25 mg, and prazosin, 5 mg each three times daily. He continued to take cholestyramine; lovastatin, 40 mg qd; niacin, 1000 mg; glyburide, 1.25 mg daily, was added a year or so ago. Home blood pressure readings ranged between 140/75 mm Hg and 155/80 mm Hg. Ambulatory blood pressure readings indicated average values of 149/83 mm Hg. Serum creatinine was 2.2 mg/dl; creatinine clearance, 38 ml/min. Amaurosis fugax developed at age 69, which carotid endarterectomy corrected without complications. He continued to smoke. He completed radiation therapy for carcinoma of the prostate, for which he now has no evidence of disease. A magnetic resonance angiogram (MRA) with gadolinium contrast medium was performed to determine progression (or not) of the vascular lesions (Fig. 2). Aneurysmal dilation above the previous graft remained visible, but no progression in the renal artery lesions per se could be seen.

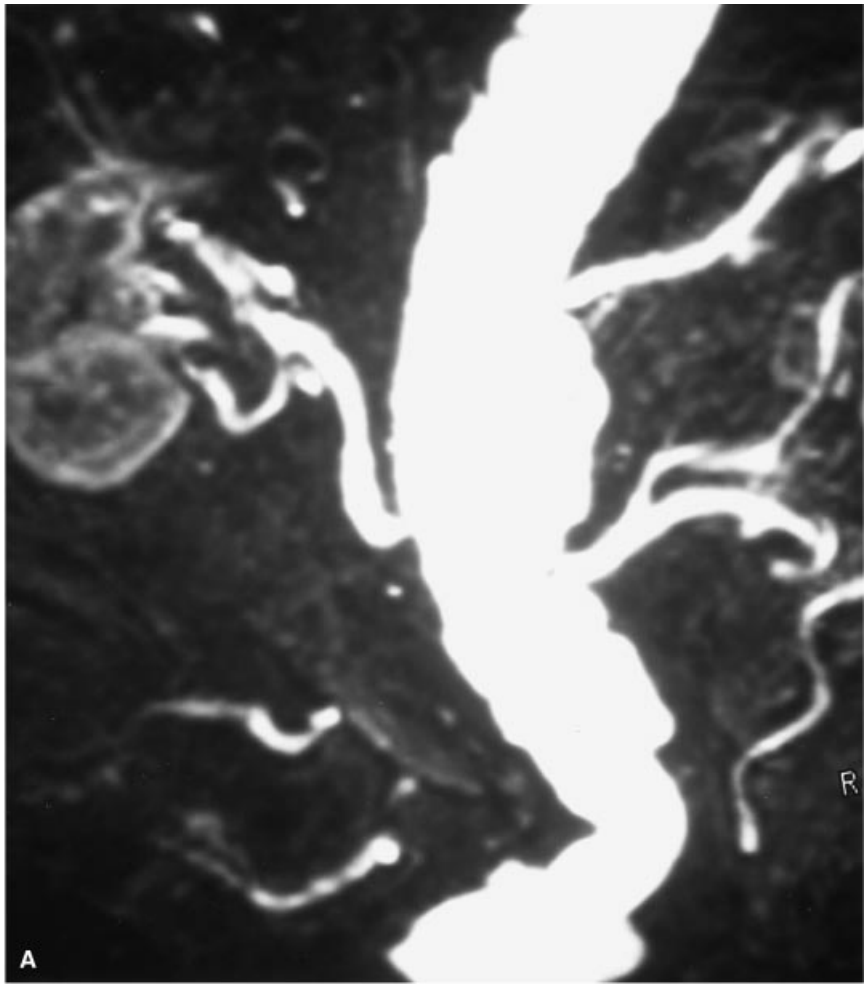
DISCUSSION

DR. STEPHEN C. TEXTOR (*Consultant, Division of Hypertension, Mayo Clinic; and Associate Professor of Medicine, Mayo Medical School, Rochester, Minnesota*): The patient presented here illustrates several vexing questions raised regularly to nephrologists and internists by patients with atherosclerotic vascular disease. At the initial referral, this patient's hypertension was accelerating, almost certainly related to renal artery stenosis. Renal-vein-renin determinations suggested more severe stenosis to the right kidney, but renin values were elevated on both sides, and stenosis was present bilaterally. This patient faced the risk of bilateral progression and a continued decline in renal function; some have termed this condition "ischemic nephropathy" [1–3]. Renal revascularization can improve blood pressure control and sometimes forestall progressive vascular compromise to the kidneys, but the hazards of surgical revascularization were substantial in this patient; he had extensive aortic disease, previous abdominal aortic reconstruction and, later, symptomatic carotid artery disease. The initial decision regarding management of his renovascular disease was complicated further by newly identified prostatic cancer. The clinical judgment regarding renal revascularization therefore reflected a complex balance of risks and benefits.

Key words: stenosis, hypertension, atherosclerosis, ischemia, surgical revascularization

The Nephrology Forum is funded in part by grants from Amgen, Incorporated; Merck & Co., Incorporated; Hoechst Marion Roussel, Incorporated; Dialysis Clinic, Incorporated; and R & D Laboratories, Incorporated.

Fig. 1. Contrast aortogram at age 66 (*A*) and selective right renal artery injection (*B*). The previous aortic graft is visible in the infrarenal aorta. Aneurysmal dilation of the aorta above the graft can be seen, from which the renal arteries arise. A high-grade stenosis with post-stenotic dilation of the right renal artery is present. Moderate stenosis of the left renal artery is present. Renal vein renin measurements demonstrated bilateral release of renin, although more pronounced from the right (see text). Arrows indicate vessels with proximal stenoses.



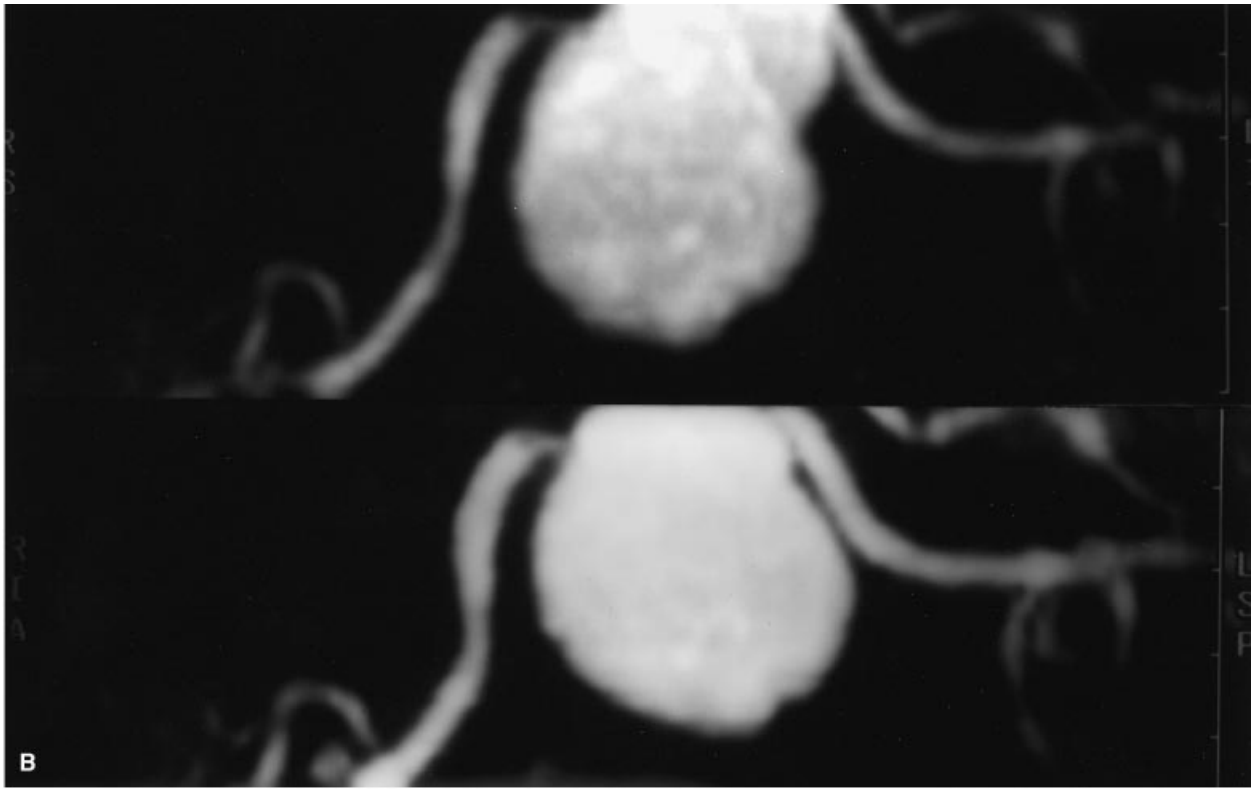


Fig. 2. Magnetic resonance angiogram with gadolinium contrast obtained three years later. Aortic dilation above the previous graft is still visible, and the stenotic lesion in the right kidney has not changed appreciably during this interval. Sagittal reconstruction of the image demonstrates the origin of the renal arteries, with severe obstruction on the right and only modest narrowing of the left, although it arises from the aneurysmal segment.

My objective today is to examine the changing characteristics of patients diagnosed with atherosclerotic renal disease and renal failure, identify the risks of developing progressive renal failure attributable to renal vascular disease, and to consider the risks and clinical outcomes of surgical revascularization in these patients. As a practical matter, the decision about whether to proceed with renal revascularization hinges on an integrated assessment of these factors for each patient, combined with other considerations regarding general health and likely survival without vascular intervention.

Let me state from the outset that I believe that the value of renal revascularization remains controversial. Advances in vascular imaging, interventional radiology, and surgical revascularization have produced champions of each technology; each camp relies on data fraught with patient selection and publication biases that obscure general application. The clinical issues have been addressed from different points of view, for example, those of interventional radiologists who identify and correct vascular stenoses (without having much of a role in direct management of the patient), nephrologists who must manage end-stage renal disease and who are concerned that renovascular disease plays a causal role, and internists who must manage resistant hypertension and early renal failure. These differences in perspective sometimes hinder formulation of a cohesive understanding of progressive atherosclerotic renal artery disease. How best to recognize critical renal arterial disease in a timely manner and how to recognize when surgical intervention offers genuine benefit remain the major clinical challenges facing the physician responsible for each patient.

Effects of aging. Mortality rates for coronary artery disease and stroke have fallen steadily for the last 25 years [4]. As a result, patients above age 65 now represent a rapidly growing segment of the U.S. population; this trend is expected to continue into the next century [5]. Some researchers believe that reduced mortality from acute coronary disease permits the gradual development of critical, non-coronary atherosclerotic disease, including the abdominal aorta and renal arteries. Their view is supported by the recognition that atherosclerotic renal artery disease is becoming more common in older patients. Several studies indicate that abdominal aortic disease or renal artery stenosis, often unsuspected, is present in 15% to 23% of patients undergoing coronary angiography [6, 7]. Renal arterial disease is present in 45% to 50% of patients undergoing angiography for lower extremity peripheral vascular disease [8, 9]. Together with Dr. Hallett, my colleagues and I compared patients undergoing renal revascularization at Mayo Clinic during two time periods: 1981–1993 and the decade between 1970–1980. The average age at surgery increased substantially, as did the prevalence of associated comorbid conditions, including diabetes, congestive heart failure, and cerebrovascular disease [10]. This trend is common to many progressive diseases of our aging population [5, 11]. Thus, patients with potentially reversible, critical renal artery stenoses generally are older and more complex medically now than ever before.

Medical therapy for renovascular hypertension. The impact of new antihypertensive agents on the management of renovascular hypertension has been profound. In the 1970s, antihypertensive regimens were limited to sympatholytic agents such as methyldopa, reserpine, and guanethidine, combined primarily with thiazide diuretics. Vasodilators used later included hydralazine and minoxidil. These agents were remarkably effective in many patients, but they routinely produced onerous side effects. No agents were available specifically to interrupt the renin-angiotensin system. Most important, they failed to control hypertension in some patients, who sometimes progressed to malignant hypertension with loss of renal function. Presentation with accelerated hypertension, including both grade III (retinal hemorrhages) and IV (papilledema) retinopathy, was attributable to renovascular hypertension in as many as 32% of patients in the 1970s, at least in whites [12]. In the 1970s, even bilateral nephrectomy was used as a lifesaving procedure to relieve malignant hypertension [13, 14].

Both angiotensin-converting-enzyme (ACE) inhibitors and calcium-channel-blocking agents became widely available in the early 1980s. Hollenberg reviewed the impact of ACE inhibitors on renovascular hypertension [15, 16]. Before the advent of this drug class, medical treatment controlled blood pressure in fewer than 46% of patients (usually defined as blood pressure levels below 160/90 mm Hg) [16]. But the availability of ACE inhibitors resulted in excellent blood pressure control in 82% to 95% of patients in prospective series [17, 18]. Under some conditions, ACE inhibitors can reduce glomerular filtration rate, particularly in patients with renal artery stenosis [19, 20]. However, GFR does not usually fall in patients with unilateral disease, even in those with surgically proven renovascular hypertension [21]. Although this phenomenon is well known [22], the fraction of patients with even high-grade bilateral renal artery stenosis in whom renal function significantly declines is on the order of 25% to 38% [21]. Calcium-channel-blocking agents, another potent group of agents, have been remarkably well tolerated and effective, as compared to medications used previously. Additional classes, including the angiotensin-receptor-blocking agents (for example, losartan), continue to expand therapeutic options. The concept of urgent, bilateral nephrectomy as a therapeutic consideration for patients with accelerated hypertension has virtually disappeared.

One rarely appreciated result of improved medical therapy is that many patients with renovascular hypertension now are never identified. Recent recommendations from the Joint National Committee (JNC) of the National High Blood Pressure Education Program argue for minimal laboratory investigation of patients whose blood pressure is well controlled and whose renal function is stable [4]. As I will discuss momentarily, many patients with identified renal artery stenosis can be managed satisfactorily with current medical antihypertensive regimens.

Thus, renal revascularization for controlling or "curing" renovascular hypertension is currently less pressing than a decade ago. The patient under discussion today illustrates how medical therapy can be used to satisfactorily control blood pressure. But some interventionists are concerned that even though the blood pressure may be controlled, loss of renal function still might progress. A critical question thus is: what are the risks of progressive renal artery stenosis and progressive renal failure as compared to the risks of revascularization?

Progressive renal artery stenosis and renal failure. Atherosclerotic disease of the renal arteries is a progressive disorder [23, 24]. Early studies identified progression to renal artery occlusion in 44% to 50% of patients followed for five years [25, 26]. Duplex ultrasound studies indicate that 24% of stenotic lesions with more than 60% luminal narrowing advance over fourteen months and such vascular progression is associated with loss of renal volume [27, 28]. Some clinicians have interpreted these data as mandating early intervention, for example, angioplasty on any "significant"

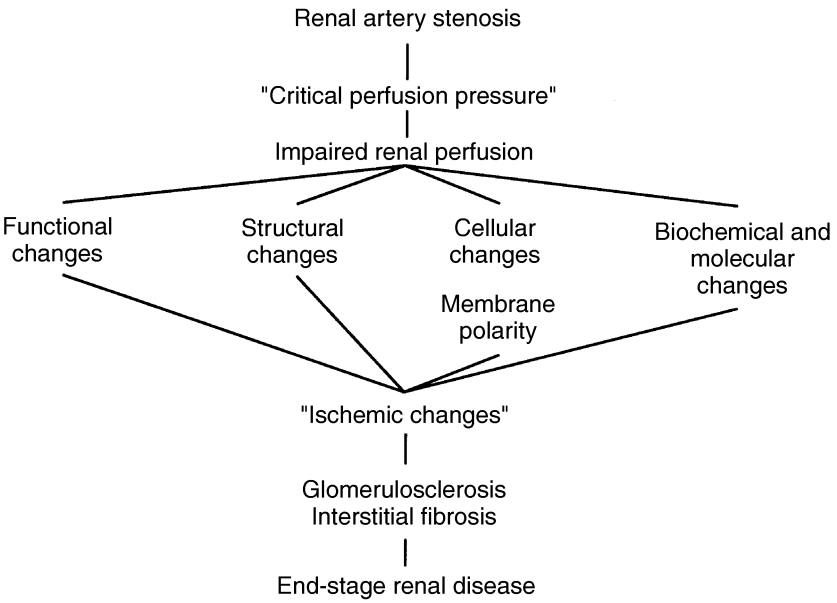


Fig. 3. Paradigm by which critical renal artery stenosis can lead to irreversible renal injury. Central to this discussion is the concept that restoration of renal perfusion may allow recovery or preservation of renal function. At some point, however, these changes become irreversible. The sequence of events leading to irreversible change is poorly understood.

lesion [29, 30]. But we should keep in mind that the same data indicate that more than one-half of patients do not progress during the same interval. Whether similar rates of progression will be encountered in the future, particularly with improved antihypertensive therapy, decreased tobacco use, and more intensive lipid reduction, is not certain [31]. But preliminary reports of patients with known bilateral renal artery disease randomized to either medical or surgical therapy indicate that rates of progression are less than a decade ago [32, 33].

As many as 15% of patients over age 50 who reach end-stage renal disease (ESRD) have underlying atherosclerotic renal artery stenosis without other primary renal disease [23, 24]. The concept that critical renal underperfusion might account for their dialysis requirement is supported by occasional reports of renal revascularization that leads to recovery of sufficient renal function to allow the patient to discontinue dialysis [35, 36]. Enthusiasm for revascularization in patients with atherosclerotic disease must be tempered, however, both by the risks and costs involved, and even more importantly by major gaps in our understanding of which patients are likely to recover renal function and benefit from taking those risks.

Pathophysiology of "ischemic nephropathy." A large body of research regarding renal underperfusion leading to renovascular hypertension dictates clinical practice. Reviews of this subject have been presented elsewhere [37, 38]. Hypertension in patients with renal artery stenosis is mediated by multiple effector mechanisms, including the renin-angiotensin system, sympathetic nervous pathways, and alteration of the balance among nitric oxide, eicosanoids, and other vasoactive systems [39, 40]. While important questions remain, particularly regarding long-term adaptation to vascular stenoses, the availability of animal models and intense research activity have produced sufficient information to allow us to rationally address renovascular hypertension in humans.

Unfortunately, substantive data related to the pathophysiology of parenchymal renal failure during chronic underperfusion of the kidney are much more limited [41, 42]. The importance of our need to better understand this process cannot be overstated. Recent reviews highlight potential mechanisms by which intermittent, non-sustained regional underperfusion within the kidney might alter cell polarity and structure, initiate cytokine release, and activate interstitial fibrosis [43, 44]. Whole-organ measurements of oxygen consumption suggest, however, that true "ischemia," that is, a deficit of oxygen delivery, does not develop, even in severely underperfused kidneys [45, 46]. In view of the kidney's large filtering function, it is vastly overperfused in terms of oxygen delivered. Hence the term "ischemic nephropathy" carries assumptions that have neither been tested nor confirmed. The possibility of local intrarenal areas of true ischemic injury cannot be excluded.

Figure 3 illustrates a general paradigm by which impaired renal perfusion leads to interstitial fibrosis and renal failure. The details of what cellular mechanisms induce irreversible parenchymal injury in this condition remain to be fully elucidated. A central element to this paradigm is that restoration of arterial perfusion to the kidney beyond a critical stenosis can restore renal function. Unfortunately, renal function does not recover uniformly. Under some conditions, loss of renal function beyond a stenotic lesion leads to irreversible parenchymal injury. Thus, understanding the mechanisms by which renal failure occurs, or at least identifying when renal function is no longer salvageable, likely will be essential for the rational application of vascular restoration in patients.

Outcomes of renal revascularization in azotemic patients. Several investigators believe that preservation of renal function and improvement in blood pressure control are indications for renal revascularization [47, 48]. Results regarding blood pressure control should be considered separately from changes in renal function. We have reviewed the experience at Mayo Clinic dating back to 1970 regarding both angioplasty and surgical revascularization [10, 49].

Does renal revascularization in fact return blood pressure to normal levels? Initial attempts at both surgical bypass, and later percutaneous transluminal renal angioplasty (PTRA), focused on

"cure" of hypertension. Considerable effort was directed toward establishing that the renal artery stenotic lesions were responsible for hypertension [37, 50]. Hence a series of functional studies including side-to-side comparisons of renal function were developed. Most recently, side-to-side comparisons of renal vein renins have been employed to identify the responsible "pressor" kidney [51]. Such functional studies indeed provided support for surgical intervention when strong lateralization was demonstrated [52–54]. Remarkably, several series suggested that even when renal vein values did not lateralize, improved blood pressure control was likely in more than one-half the cases [54, 55].

These "side-to-side" diagnostic studies are less commonly employed today because of three main reasons. (*1*) Improved blood pressure control is rarely the foremost consideration for revascularization. (*2*) The concept of "cure" in atherosclerotic renovascular disease has been tempered. Renal revascularization reduces but rarely eliminates the requirement for antihypertensive drug therapy [56–58]. (*3*) Some improvement in blood pressure control is evident even in patients without lateralizing renal vein renin studies. Most patients with atherosclerotic disease have long-standing hypertension, which remains even after the pressor effects of an underperfused kidney are removed. Hence, the number of medications falls, on average, from 2.6 to 1.4 antihypertensive medications per patient, but rarely to zero [49, 58]. Reported cure rates for hypertension related to atherosclerotic disease range from 13% to 55% of patients [58, 59]. In sum, improved blood pressure control with less medication is a realistic goal of renal revascularization.

Can revascularization restore renal function? The answer is yes, but accurately predicting changes in renal function after either surgical revascularization or renal angioplasty is among the most difficult problems in this field. Although small series and isolated cases demonstrate the possibility of excellent recovery of renal function, such results are infrequent. Patients with nearly normal renal function (usually defined as a serum creatinine concentration less than 1.5 mg/dl) have little long-term change in serum creatinine after surgical revascularization or PTRA [47, 56, 59]. We evaluated the effects of renal revascularization in patients with serum creatinine levels of 2.0 mg/dl or higher. The overall results of 253 patients with atherosclerotic disease (out of 320 total patients with a variety of diseases) undergoing PTRA have been published previously [49]. Of these 253, 44 were azotemic at the time they underwent PTRA. Several features in our experience (shared by others) merit consideration [49]. Figure 4 illustrates changes in serum creatinine before and after PTRA both in azotemic (n = 44) and nonazotemic patients (n = 209). Preintervention serum creatinine values in azotemic subjects were 3.47 ± 0.25 mg/dl and were 3.36 ± 0.28 mg/dl at last followup (NS). Group values, however, obscure the real clinical outcomes in this situation. Figure 5 shows individual serum creatinine values for the 44 azotemic patients. In our review of renal outcomes, we divided patients into groups according to a clinically meaningful change in renal function: Group A (fall in serum creatinine ≥ 1.0 mg/dl), Group B (change in serum creatinine < 1.0 mg/dl), and Group C (rise in serum creatinine ≥ 1.0 mg/dl). Panel A depicts 12 patients who had major improvements in serum creatinine (4.82 ± 0.60 mg/dl to 2.42 ± 0.34 mg/dl), Panel B shows the 23 patients who had no change (2.90 ± 0.25 mg/dl to 2.91 ± 0.32 mg/dl), and Group C represents the 9 who had a major loss of renal function (3.09 ± 0.24 mg/dl to 5.73 ± 0.44 mg/dl). As the figure indicates, changes in renal function were not always evident immediately after PTRA, but were evident at later followup review (mean followup, 21 months). The 9 patients with deteriorating renal function had poor clinical results: 8 of the 9 required dialytic support or died within one year after the procedure. No technical features (that is, patency rates or success at dilation) were evident to account for differences among the groups. In some cases, embolic changes evident in other vascular beds, including the feet and skin, suggested that atheroembolic disease was responsible for renal deterioration in many of these individuals.

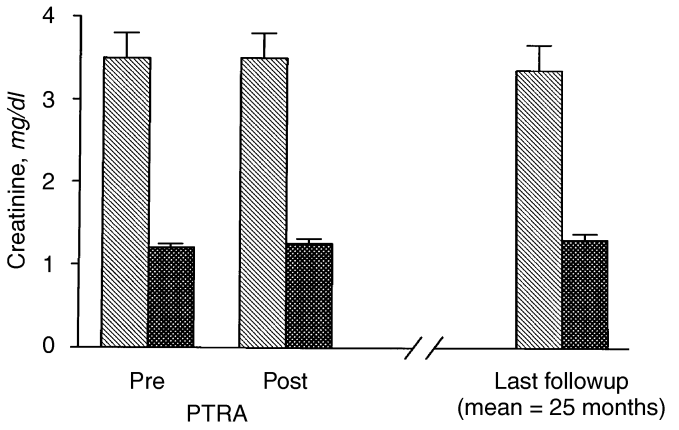


Fig. 4. Serum creatinine levels before ("pre"), immediately after ("post"), and at last followup (mean, 25 months) in 253 patients with atherosclerotic disease undergoing percutaneous transluminal renal angioplasty (PTRA). Symbols are: (▨) creatinine ≥ 2.0, $N = 44$; (▩) creatinine < 2.0, $N = 209$). Group mean values demonstrated no change overall, either in patients with pre-existing renal failure or patients with normal renal function.

A review of the procedures and results of 304 azotemic patients undergoing surgical renal revascularization during the same time interval (1980–1993) has been published from our institution. Remarkably, the average serum creatinine values and the proportions falling into each outcome category were similar to those who had undergone PTRA [10, 49]. Among 304 patients with serum creatinine levels above 2.0 mg/dl, 28% of patients (84 of 304) had a meaningful improvement in renal function, defined as a reduction in serum creatinine level of 1.0 mg/dl. Most (52.6%, or 106 of 304) had no change, defined as a change in serum creatinine of < 1.0 mg/dl. Creatinine levels rose more than 1.0 mg/dl in a substantial percentage (19.7%, or 60 of 304) after surgical revascularization; this increase reflected a clinically important loss of renal function.

Regardless of the means of revascularization, long-term renal function can significantly improve or it can deteriorate. Even authors who favor PTRA differentiate between "technical success," successful establishment of a patent renal artery lumen, and "clinical success," that is, improved renal function [47]. The two results do not necessarily co-exist. Hence, studies invariably contain a group in which "technical success" is accompanied by clinical deterioration. In several series of surgical patients, renal functional outcomes in atherosclerotic patients were mixed, and serum creatinine values generally did not change [57, 58, 60–62]. Most series report renal function as "improved" or "stable," in effect, comparable to our groups (Fig. 5 A and B). If renal

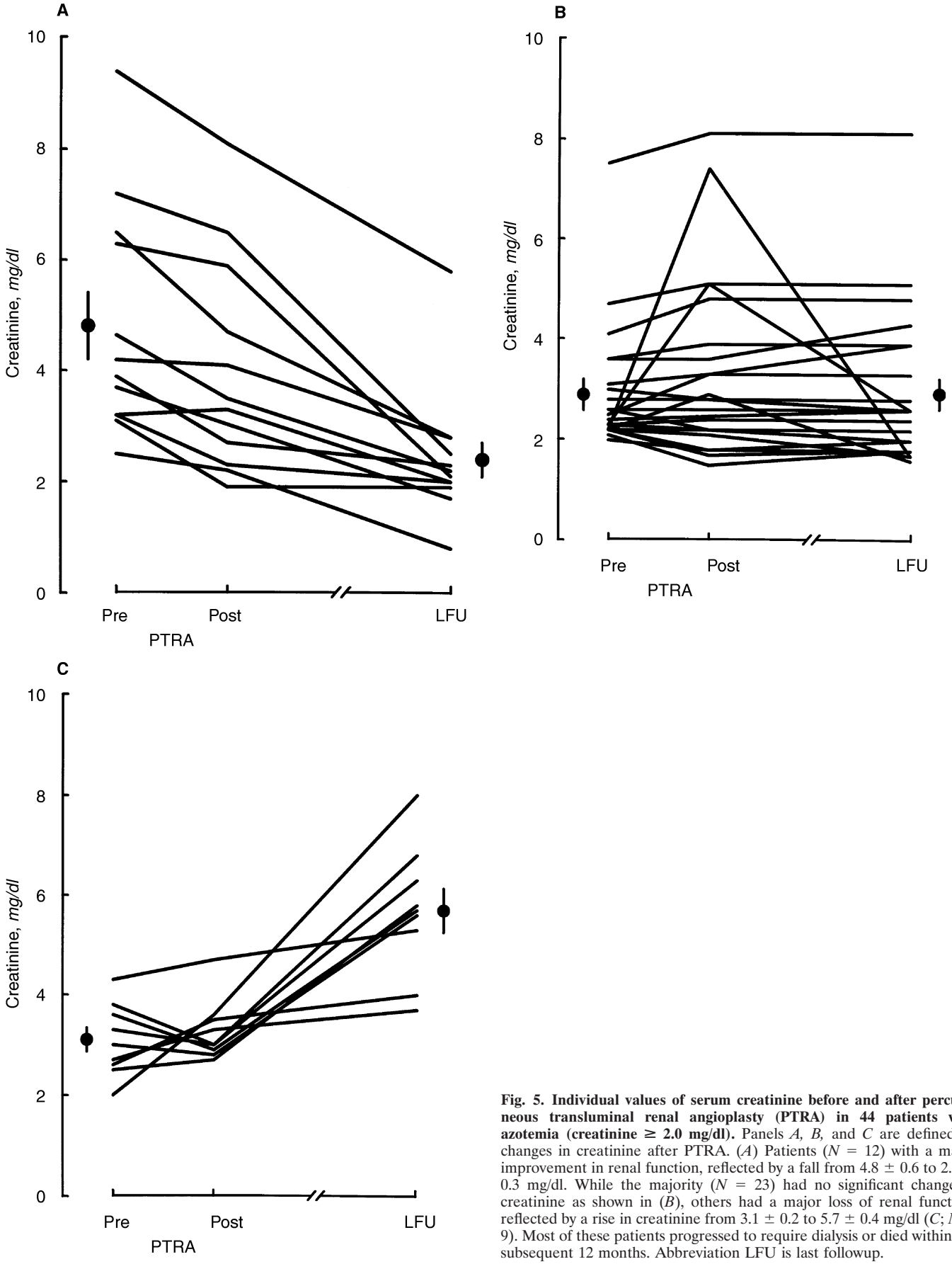


Fig. 5. Individual values of serum creatinine before and after percutaneous transluminal renal angioplasty (PTRA) in 44 patients with azotemia (creatinine ≥ 2.0 mg/dl). Panels *A, B,* and *C* are defined by changes in creatinine after PTRA. (*A*) Patients ($N = 12$) with a major improvement in renal function, reflected by a fall from 4.8 ± 0.6 to 2.4 ± 0.3 mg/dl. While the majority ($N = 23$) had no significant change in creatinine as shown in (*B*), others had a major loss of renal function, reflected by a rise in creatinine from 3.1 ± 0.2 to 5.7 ± 0.4 mg/dl (*C*; $N = 9$). Most of these patients progressed to require dialysis or died within the subsequent 12 months. Abbreviation LFU is last followup.

function improves in some and yet overall mean values do not change, clearly there are patients whose renal function deteriorates, although this point is often not addressed directly.

Does renal functional change affect overall patient outcome? As one would anticipate, the answer is yes. Patients with a major loss (defined as $\geq$ 1.0 mg/dl) of renal function (between 20% and 25% of patients in most series) are likely to need dialytic support, both acutely and chronically. Chaikof and colleagues emphasized the importance of improved renal function when they recognized that long-term patient survival was closely related to glomerular filtration rate soon after renal revascularization [61].

Deterioration of renal function after vascular intervention is not rare. The exact basis of the loss of renal function is not clear, although atheroembolic renal disease undoubtedly plays a role. Thadhani et al reviewed the clinical course of 52 patients with histologically proven atheroembolic disease following angiography and found gradual progression to renal failure; that is, 23 of 52 patients (44%) required dialysis within 6 months [63]. Nevertheless our limited understanding of the precise cause of parenchymal renal injury beyond renal artery stenosis is a major handicap in this regard. We cannot exclude the possibility that sudden restoration of perfusion pressure, which perhaps generates toxic free radicals or oxygenated species, exposes the kidney to further injury after revascularization. Hence, we should carefully weigh the possible risks and benefits of revascularization.

Given all these results, what pre-intervention data best assist us in predicting the results of renal revascularization? Our experience suggests that distinguishing between "early survival" (within 30 days of surgical revascularization) and "late" survival (beyond 30 days, assuming survival to that point) is helpful. As expected, early surgical risk is most closely related to the magnitude of the procedure (that is, whether concurrent aortic reconstruction is attempted) and to the presence of active cardiovascular disease, that is, congestive heart failure, angina, or cerebrovascular disease. In our series of 304 patients, early survival (30 days or less) did not depend on pre-operative levels of renal function, age, or other clinical variables [64].

Late survival (beyond 30 days) depended on other factors. Pre-operative level of renal function (as defined by 1/creatinine), age above 70 years, and the presence (not repair) of an aortic aneurysm independently predicted shortened survival. These data are consistent with other reports suggesting that patients with more advanced levels of renal failure rarely have major improvements in function [24, 36, 62, 65]. The presence of diabetes did not independently predict shortened survival, but it did independently relate to duration of hospitalization and costs of the procedure [66]. We used a Cox proportional hazards model to predict renal functional outcome using a late serum creatinine above 4.0 mg/dl as an end point. In this instance, the strongest predictors of deteriorating renal function were (*1*) pre-operative serum creatinine, (*2*) male gender, (*3*) aortic repair, and (*4*) an inverse relationship to congestive heart failure [66].

An integrated approach to the patient with atherosclerotic renal artery disease. How do the internist and nephrologist apply this information to patients such as the man presented today? My recommendation is that we treat such patients individually; close evaluation should monitor changes in renal vascular lesions, renal function, and blood pressure. If disease progression is evident and other, patient-specific, risk factors favor long-term survival, then renal revascularization should be considered. Our data and those of others favor initiating this process before advanced renal dysfunction is evident. Hence, we believe that the "window of opportunity" is defined by serum creatinine levels between approximately 1.5 mg/dl and 3.0 mg/dl for most surgical revascularization. Our interpretation recognizes that waiting for advanced renal failure to develop diminishes the likelihood that renal function will improve after revascularization. Several series suggest that serum creatinine levels above approximately 3.0 mg/dl are associated both with poor renal and patient outcomes. These data also must be considered in light of relatively poor survival with hemodialysis in such patients [23].

Conversely, patients with nearly normal renal function and well-controlled blood pressure gain relatively little more from renal revascularization. Cure rates are limited in patients with atherosclerotic disease, so continued antihypertensive therapy likely is necessary. Withholding either PTRA or surgery avoids exposing these patients to the immediate risks and costs of these procedures, which may never be needed. Results of several recent prospective series support this impression. Preliminary results from Scotland indicate no major benefit in renal function in patients randomized to PTRA as compared to medical therapy [32].

Patients with atherosclerotic renal artery disease continue to present major challenges to internists and nephrologists. This is an expanding problem, as the U.S. population ages and renal artery lesions appear in older patients with more widespread problems and limitations. There is a pressing need to more closely examine prospectively the role of vascular disease in producing chronic renal failure. Until these studies are available, managing such patients requires an intensely individualized approach, as I have tried to outline today.

QUESTIONS AND ANSWERS

Dr. John T. Harrington (*Dean, Tufts University School of Medicine, Boston, Massachusetts*): Steve, you told us that serum creatinine fell from about 4 mg/dl to 2 mg/dl in 28% of the patients operated on in your series. Could you propose a way that would currently identify that quota of the patient population? Second, can you speculate on what you'd like to look at to try to better identify that 27% in the future?

Dr. Textor: The simple answer is "no." We have no specific way of identifying patients whose renal function will improve after revascularization. In 1985, we reported in the *Annals of Internal Medicine* that we had used nitroprusside to reduce blood pressure in a stepwise fashion. We were able to identify a "critical perfusion pressure" at which blood flow to the kidneys fell sharply. Those patients regained blood flow after we revascularized even one kidney. That method constitutes a "stress test" to the kidney and does identify critical stenoses, but it is technically difficult. There are a few clinical predictors, although they are weak. A rapid rise in the serum creatinine concentration immediately before clinical diagnosis of renal artery stenosis may be a positive sign for recovery of renal function. In a multivariate analysis, renal function after revascularization improved more in patients with congestive heart failure than in others [67]. The reason is not clear; we can only suppose that part of the renal impairment is due to pre-renal azotemia and that some of the benefits of renal revascularization also reflect improved cardiac function.

We are undertaking studies with the goal of predicting clinical responses. In renal biopsy specimens examined at the time of

surgical revascularization, the degree of interstitial fibrosis tends to be the best predictor of functional recovery, as with most other renal diseases. What governs interstitial fibrosis during poststenotic underperfusion of the kidney is not clear, but we suppose that multiple factors participate, including angiotensin II, oxidative stress, and stimulation of cytokines.

Dr. Nicolaos E. Madias (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): You compared patients who were treated with surgery at Mayo Clinic in the 1970s and early 1980s with those who were treated in the late 1980s and early 1990s. One major difference between the two groups must be the variable use of ACE inhibitors. The issue is, when you tabulated renal function at baseline or at followup, was a component of functional azotemia present due to ACE inhibition? How did you deal with this phenomenon either before or after the intervention?

Dr. Textor: That is an important question. We did construct a database including medications before and after surgery. Let me emphasize that our patient group all had serum creatinine levels $\geq$ 2.0 mg/dl. With the recognition that ACE inhibitors could produce acute functional renal insufficiency, the prevailing concept in the 1980s was that these agents should be avoided in patients with renal insufficiency. As a result, remarkably few—approximately 17%—were taking ACE inhibitors before surgery. Thus, the use of ACE inhibitors did not appear to have been an important factor in these patients. It is possible that some patients had earlier exposure to ACE inhibitors and perhaps developed a temporary loss of GFR that prompted withdrawal of the drugs. I cannot tell much about that from our data.

Dr. Madias: As you indicated, the reason that we opt for revascularization is the concern that progressive renal dysfunction will occur. Yet, as you noted, a number of patients don't experience this problem. In my own practice, I have been impressed by the fact that a sizeable number of patients I have followed for a long time, who had severe bilateral renovascular stenoses or renal artery stenosis in a solitary kidney and had either refused or failed intervention, actually maintain remarkably stable renal function. Could you please expand on our knowledge about the natural history of untreated advanced renovascular disease, particularly on existing controlled, prospective data?

Dr. Textor: The natural history of atherosclerotic renal artery disease is somewhat controversial. In the early 1980s, Novick and associates emphasized revascularization's potential for preserving renal function [see Ref. 24]. This possibility seemed especially important in view of several retrospective series suggesting that between 40% and 50% of lesions progressed over relatively short time periods [25, 26]. Few prospective data are available, however, particularly recently, when more attention has been paid to vascular risk factor intervention, such as lipid reduction and withdrawal of smoking. To their credit, the Cleveland Clinic group has enrolled patients in a prospective, randomized study of progressive renal artery disease. The results of this trial have not yet been published, but preliminary discussion with the investigators indicates that current rates of progression have not been as high as predicted. These data are consistent with other recent trials comparing renal angioplasty with medical therapy and with other recent investigations using Doppler ultrasound studies in atherosclerotic disease [32, 68, 69]. All these data suggest that rates of disease progression to critical levels are less than earlier studies suggested, more on the order of 20% to 25% over 3 years.

Dr. Geetha Narayan (*Division of Nephrology, St. Elizabeth's Hospital, Brighton, Massachusetts*): I have two questions. What has been the experience at your institute with respect to angioplasty with and without stents? Also, could you comment on your incidence of complications, especially atheroembolic, with respect to these procedures? To expand on that question, is there a correlation between these complications and the degree of aortic disease as we saw in this gentleman? Should the magnitude of the aortic disease be a determinant of who should not subjected to the procedure?

Dr. Textor: We are entering an era of stents. Our own experience does support the use of stents in some situations, particularly with ostial lesions that fail angioplasty. Our interventional radiologists are conservative in this regard, in part because currently few long-term data exist regarding outcomes, although a recent paper from Germany does support the relative safety of stents [70]. Once stented, however, the vessel is never the same. If surgical intervention is needed later, the option of repairing a stented vessel is limited. Occasionally, stents have migrated out of position and protrude into the aorta. I am confident that most of these problems will be overcome as technology advances. But let me emphasize that clinical results related to blood pressure and changes in renal function—both favorable and unfavorable—are not related directly to which method of revascularization is chosen. Furthermore, none of these procedures avoids the risk of atheroembolic events.

Dr. Mark E. Williams (*Division of Nephrology, New England Deaconess Hospital, Boston, Massachusetts*): Getting back to the role of ACE inhibitors, both diagnostically and therapeutically, do you think the behavior of renal function in response to acute ACE inhibitor therapy provides any predictive information about the likelihood of long-term benefit with revascularization?

Dr. Textor: That is a good question. It reflects the hope in the early 1980s that the blood pressure response to ACE inhibitors would predict surgical outcomes. Several published series addressed this point by administering ACE inhibitors to patients with known renal artery disease. In the series by Jackson et al, the incidence of acute renal dysfunction (defined as a tripling of serum creatinine) was 38% in patients with bilateral disease and 0% in patients with unilateral disease [71]. This result can be interpreted several ways, but the study makes the point that in at least 60% of patients with bilateral renal artery stenosis, renal function did not worsen despite ACE inhibition. I know of few data using ACE inhibitors that predict general response to renal revascularization, but observation of serious renal deterioration certainly raises the clinical likelihood of high-grade stenosis to the entire functional renal mass. Failure to detect such a decrement, however, does not exclude bilateral disease.

Dr. Williams: Could you speculate about long-term therapy with ACE inhibitors in renovascular disease in its milder forms: do you think they are likely to be particularly beneficial or nefarious?

Dr. Textor: That is a critical question, of course, particularly with the broadening indications for the administration of ACE inhibitors, as in patients with congestive cardiac failure. Some authors take the position that administration of ACE inhibitors to patients with renal artery stenosis leads to an irreversible fall in GFR in the affected kidney, thereby constituting a "medical

nephrectomy" [72]. I disagree with this interpretation. The likelihood of excellent blood pressure control without clinically important deterioration of renal function in patients with renal artery stenosis has been excellent [16, 17]. Several experimental studies suggest that functional deterioration of GFR attributable to ACE inhibitors can be reversed so long as blood flow remains adequate; we have reviewed this topic [22]. Of course, severe occlusive vascular disease leading to impaired blood flow beyond a critical point can lead to tissue underperfusion and permanent thrombosis. In general, the notion that ACE inhibitors pose a particular hazard in this setting has been overstated. A reassuring observation in this regard is the remarkable success in administering ACE inhibitors to patients with advanced left-ventricular dysfunction, as in the CONSENSUS and SAVE trials. Such patients have a relatively high frequency of underlying, often unsuspected, renal artery stenosis [7]. Despite this condition and the fact that such patients may be prerenal, relatively hypotensive, and treated with diuretics, the incidence of significant renal functional deterioration is remarkably low.

Dr. James Strom (*Division of Nephrology, St. Elizabeth's Hospital*): With the large experience that you've had with diagnostic and selective arteriography, can you comment on the frequency of hemodynamically significant renovascular disease versus arteriolar nephrosclerosis as the cause of gradually progressive chronic renal failure? Should we approach both disorders conservatively and not investigate at all?

Dr. Textor: How often slowly progressive renal failure represents large-vessel arterial stenosis is not known precisely. We have prospectively studied patients who, based on clinical risk factors and an asymmetric preliminary study, for example, abnormal captopril renogram or differential renal size by KUB or ultrasound, are considered at high risk for underlying renal arterial stenosis [73]. Remarkably, the incidence of renal artery stenosis defined by subsequent angiography rarely exceeds 55%. Hence, despite high clinical suspicion, a substantial portion of patients have normal angiograms and abnormal renal function apparently attributable to small-vessel disease or other causes. I believe that our observations reflect many others' experience.

Dr. Richard Kopelman (*Division of General Internal Medicine, New England Medical Center*): I have two questions. When confronted with a patient whom you've decided to revascularize, how do you decide between surgery and angioplasty? My second question is: In the patient whom you've decided to follow medically, what parameters do you follow?

Dr. Textor: Those are practical questions. First, few studies have systematically compared renal angioplasty versus surgery for complex disease. A single Scandinavian study found similar efficacy for both therapies in unilateral disease, although the recurrence rate and need for further procedures was higher in patients subjected to PTRA [74]. Most institutions depend on local expertise in making such judgments. At our institution, we feel fortunate to have excellent interventional radiology and vascular surgery, which we view as complementary approaches. Angioplasty is generally good and becoming better, but I am concerned about the long-term durability of revascularization by this means. Conversely, surgical revascularization poses considerable immediate expense and some risk despite its proven long-term efficacy.

Regarding followup during medical therapy, we currently utilize the parameters that would affect our management: careful assessment of blood pressure control and renal function. If these two variables are stable, no further studies are necessary.

Dr. Andrew S. Levey (*Division of Nephrology, New England Medical Center*): I want to ask you more about atherosclerotic renal vascular disease as a predictor of progressive renal failure. Not only are there few prospective studies, but most of the retrospective studies aren't very good. The definition of the patients is always altered by selection, which can't be completely explained. Even the retrospective studies don't explain this disease. Rarely would we operate on people for control of blood pressure. What we really need to think about is preventing renal failure. I don't mind if the patient has a serum creatinine level of 2 or 3 mg/dl so long as they can stay off dialysis and out of heart failure. Are these noninvasive tests, such as the duplex sonogram or MRA with gadolinium, sensitive enough to detect renal lesions? Have studies been conducted to determine renal vascular disease in a dialysis population, or alternatively in patients with renal insufficiency, for example, patients with a serum creatinine level of 3 mg/dl or more?

Dr. Textor: How best to identify patients with occult renal artery stenosis is not known. Some instititions have developed particular expertise with Doppler ultrasound and recommend screening patients with advanced renal disease using that method [75, 76]. Most other institutions have not achieved a high level of confidence with this method. Our own sonographers still report failure rates in as many as 20% of patients studied. Magnetic resonance angiography is improving rapidly, particularly with the use of nontoxic contrast media. Perhaps this technique will improve our ability to detect such lesions.

Let me offer another caveat. Identifying a vascular lesion in a patient with renal failure does not assure the clinician that this lesion is responsible for the patient's declining renal function. Nor does it predict whether a patient will recover renal function after revascularization. How to determine the latter needs considerable further study.

Dr. David Cahan (*Chief of Nephrology, Faulkner Hospital, Boston*): Could you comment on age as an independent risk factor for renal revascularization? In community practice, nephrologists often encounter suspected renal vascular disease in patients well into their 70s and 80s. Second, what is the utility of a simple test such as ultrasonography in determining "how small is too small" a kidney to revascularize?

Dr. Textor: Age is an important consideration. Impressive advances in surgical technique and peri-operative support services, including anesthesia and intensive care, mean that most people can survive even complex surgical procedures. Of course, reported series often include subjective screening and patient selection biases that cannot be measured precisely. Age is an important predictor of *long-term* survival, however, and the net benefit from performing surgical procedures decreases as a result of competing risks from other age-related diseases [77]. Most of us realize this intuitively, although articulating this with our patients and their families is often difficult.

Regarding identifying kidneys beyond salvage, many authors have offered renal size as a possibility, arguing that radiographic size less than 8 cm (based on a film of the abdomen; ultrasound length would be smaller) means little chance of recovery. But many exceptions exist, and we need more precise methods of identifying kidneys worth revascularizing.

Dr. Ronald Perrone (*Division of Nephrology, New England*

Medical Center): I was intrigued by your initial comment that one of the patient syndromes that stimulates you to think about renal artery disease is that of recurrent flash pulmonary edema. It reminds me of a patient whose unstable angina was cured with renal angioplasty. Do you think there are mechanisms other than controlling hypertension or improving renal function and ultimately volume balance that result from successful renal artery repair?

Dr. Textor: Whether relieving renal artery stenosis affects other vascular and cardiac events is an interesting question. Studies using experimental models indicate that clamping the renal artery quickly produces a broad range of neurohormonal response [78, 79]. It activates the systemic renin-angiotensin system and induces major increases of sympathetic nerve activity and endothelium-dependent vasoactive materials, such as endothelin. All these changes have widespread effects, including the possibility of increasing coronary vascular tone. The exact means by which these mechanisms magnify each other are not understood. As you suggest, relief of critical renal artery stenosis in patients with congestive heart failure can improve symptoms beyond levels that can be explained by only improved renal function and sodium balance.

Dr. Andrew King (*Division of Nephrology, New England Medical Center*): One of the points you made was that hypertension due to renal artery stenosis is much more amenable to treatment that is renal failure on that basis. You indicate several measures that might contribute to the improved outcome of these patients. Can you focus in on lipid metabolism? With the advent of an array of lipid-reducing substances, and with the increasing recognition that some atherosclerotic lesions in the coronary vascular bed can regress with very aggressive control of lipid abnormalities, do you think that similar results might be observed in the renal vasculature? Are there any data to support that?

Dr. Textor: Let's look at the lipid question in two parts. First, is it possible that vigorous reduction of various lipid risk factors will produce regression of vascular stenoses in the kidney? Such regression has been observed in other vascular beds [80], and I see no reason why this also should not occur in the kidney. Second, is it possible that lipid-reducing therapy has other effects on the kidney? It is possible that the myriad other effects of lipid reduction via "statin"-class drugs, the HMG-CoA-reductase inhibitors, might affect the kidneys in positive ways other than causing regression of large-vessel stenotic lesions. There is a growing literature regarding the effects of lipids on accelerating the progression of primary renal disease, of course.

Dr. Strom: Might it be that a subgroup of patients that benefits from renal revascularization is "hidden" by other subgroups that cannot benefit due to irreversible glomerular sclerosis or that suffer deterioration due to cholesterol embolism or technical complications?

Dr. Textor: That is a fair question. Most surgical and angioplasty series offer some verification of technical success (or lack of obvious technical failure) before considering the procedure a failure. Cholesterol emboli may be more common than appreciated and are difficult to diagnose. Certainly patients with unidentified atheroemboli represent a "hidden" group of patients who might have benefited. The possibility that rapid restoration of renal perfusion to previously underperfused kidneys magnifies oxidative stress and results in formation of toxic free radicals [81] or another mechanism of injury cannot be excluded, of course. Both of these possibilities need further exploration.

Dr. Madias: I'd like to return to Dr. Williams' concern regarding the long-term safety of ACE inhibitors for renovascular disease. The beneficial effects of ACE inhibitors on the cardiovascular system are undeniable. As you pointed out, when patients with high-grade renovascular stenoses discontinue taking ACE inhibitors, renal function usually recovers. When renal function does not return to baseline, one can postulate that the underlying renovascular disease has progressed. Nonetheless, some experimental observations suggest that ACE inhibitors hasten ischemic atrophy of the kidney behind a renovascular stenosis [82, 83]. Could you please comment further on this issue?

Dr. Textor: Several mechanisms contribute to the loss of renal function beyond a stenotic lesion, and many of these are not understood. We studied a model in the rat using an aortic coarctation placed between the renal arteries [46, 84]. This approach offers the advantage of allowing precise measurement of post-stenotic arterial pressures. If one rapidly and drastically reduces post-stenotic pressures, the kidney stops functioning and undergoes necrosis and atrophy, regardless of additional medications. Some studies, such as those you mentioned, have administered ACE inhibitors to animals with severe renal arterial stenosis and demonstrated cortical necrosis associated with reduced blood flow [82, 83]. Other studies, including our own, demonstrate that ACE inhibition sufficient to reduce GFR without further impairing blood flow to the kidney is tolerated without permanent renal injury. Glomerular volume falls, but both structure and function recover after removal of the arterial clip or the ACE inhibitors [46, 85].

The predominant effect of ACE inhibition in humans with various stages of renal artery stenosis is not known. Perhaps ACE inhibition reduces the work of filtration and solute reabsorption, thereby buffering the kidney from the adverse effects of reduced arterial flow. However, a persistent reduction in systemic blood pressure during progressive arterial stenosis ultimately will eliminate critical blood flow and lead to permanent loss of renal function. Of course, this can go undetected because in patients with a normal contralateral kidney, the non-stenotic kidney provides adequate filtration.

Dr. Harrington: First, is there a modern decision analysis of this issue? Second, you referred to some studies that you're interested in doing looking at the factors that might cause fibrosis within the ischemic kidney. Which factors do you plan to look at, and which cytokine blockers might you employ?

Dr. Textor: That is an interesting area for application of formal decision analysis. In fact, Rimmer and his colleagues, including Dr. Madias, already have published one [86]. I was struck by the sensitivity of this analysis to the prevalence of disease in the population treated. However, one must caution that the assumptions underlying formal decision analysis schemes are limited by the fact that risk and benefits of various interventions are not distributed uniformly. Some patients are both at higher risk for disease complications and more likely to receive intervention than are others. I see no way of avoiding individualizing therapy for each patient, given the variables involved.

Regarding your second question, our group believes that underperfusion of the kidney likely activates several mechanisms that result in interstitial fibrosis. Our hypothesis is that activation of transforming growth factor-β (TGF-β), perhaps via local

production of angiotensin II and disturbed endothelial function, is a likely pathway.

DR. PERRONE: Eric Cohen speculated that there was increased development of renal cysts in ischemic kidneys [87]. Do you have any impressions or data about that?

DR. TEXTOR: I'm not aware of how this observation is manifest in patients with renal arterial stenosis.

DR. B. V. R. MURTHY (*Fellow, Division of Nephrology, New England Medical Center*): You had a cut-off of 1994 in your analysis, because you didn't want managed care to influence your model. Did you find or expect to find any influence of managed care in the overall managment of renovascular hypertension?

DR. TEXTOR: I did not discuss another important element, namely, the costs of renal revascularization, reflected by hospital stay, intensive care, surgical costs, etc. You know as well as I do that hospital stays have shortened in recent years with the advent of both managed care and extensive cost-control efforts. Until now, I have had no reason to think that managed care per se has affected our practice much in this regard. Of course, it might in the future.

Reprint requests to Dr. S. Textor, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA

REFERENCES

1. JACOBSON HR: Nephrology Forum: Ischemic renal disease: An overlooked clinical entity? *Kidney Int* 34:729–743, 1988
2. DEAN RH, TRIBBLE RW, HANSEN KJ, O'NEIL E, CRAVEN TE, REDDING JF: Evolution of renal insufficiency in ischemic nephropathy. *Ann Surg* 213:446–455, 1991
3. WILCOX CS: Ischemic nephropathy: Noninvasive testing. *Semin Nephrol* 16:43–52, 1996
4. JOINT NATIONAL COMMITTEE: The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 157:2413–2446, 1997
5. SCHNEIDER E, GURALNIK J: The aging of America: impact on health care costs. *JAMA* 263:2335–2340, 1990
6. VETROVEC GW, LANDWEHR DM, EDWARDS VL: Incidence of renal artery stenosis in hypertensive patients undergoing coronary angiography. *J Interv Cardiol* 2:69–76, 1989
7. HARDING MB, SMITH LR, HIMMELSTEIN SI, HARRISON K, PHILLIPS HR, SCHWAB SJ, HERMILLER JB, DAVIDSON CJ, BASHORE JM: Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol* 2:1608–1616, 1992
8. SWARTBOL P, THORVINGER BOT, PARSSON H, NORGREN L: Renal artery stenosis in patients with peripheral vascular disease and its correlation to hypertension; a retrospective study. *Int Angiol* 11:195–199, 1992
9. GRECO BA, BREYER JA: The natural history of renal artery stenosis: who should be evaluated for suspected ischemic nephropathy? *Semin Nephrol* 16:2–11, 1996
10. HALLETT JW, TEXTOR SC, KOS PB, NICPON G, BOWER TC, CHERRY KJ, GLOVICSKI P, PAIROLERO PC: Advanced renovascular hypertension and renal insufficiency: trends in medical comorbidity and surgical approach from 1970 to 1993. *J Vasc Surg* 21:750–759, 1995
11. HALLETT JW, JAMES ME, AHLQUIST DA, LARSON MV, MCAFEE MK, CHERRY KJ: Recent trends in the diagnosis and management of chronic intestinal ischemia. *Ann Vasc Surg* 4:126–132, 1990
12. DAVIS BA, CROOK JE, VESTAL RE, OATES JA: Prevalence of renovascular hypertension in patients with grade III or IV hypertensive retinopathy. *N Engl J Med* 301:1273–1276, 1979
13. LAZARUS JM, HAMPERS CL, BENNETT AH, VANDAM LD, MERRILL JP: Urgent bilateral nephrectomy for severe hypertension. *Ann Intern Med* 76:733–739, 1972
14. MAHONY JF, STOREY BG, GIBSON GR, ET AL: Bilateral nephrectomy for malignant hypertension. *Lancet* 1:1036–1038, 1972
15. HOLLENBERG NK: Medical therapy of renovascular hypertension: efficacy and safety of captopril in 269 patients. *Cardiovasc Rev Rep* 4:852–876, 1983
16. HOLLENBERG NK: Medical therapy for renovascular hypertension: a review. *Am J Hypertens* 1:338s–343s, 1988
17. FRANKLIN SS, SMITH RD: Comparison of effects of enalapril plus hydrochlorothiazide versus standard triple therapy on renal function in renovascular hypertension. *Am J Med* 79(Suppl 3c):14–23, 1985
18. TEXTOR SC: ACE inhibitors in renovascular hypertension. *Cardiovasc Drugs Ther* 4:229–235, 1990
19. HRICIK DE: Captopril-induced renal insufficiency and the role of sodium balance. *Ann Intern Med* 103:222–223, 1985
20. JACKSON B, FRANZE L, SUMITHRAN E, JOHNSTON CI: Pharmacologic nephrectomy with chronic angiotensin converting enzyme inhibitor treatment in renovascular hypertension in the rat. *J Lab Clin Med* 115:21–27, 1990
21. JACKSON B, MATTHEWS PG, MCGRATH BP, JOHNSTON CI: Angiotensin converting enzyme inhibition in renovascular hypertension: frequency of reversible renal failure. *Lancet* 1:225–226, 1984
22. TEXTOR SC: Renal failure related to ACE inhibitors. *Semin Nephrol* 17:67–76, 1997
23. MAILLOUX LU, NAPOLITANO B, BELLUCCI AG, VERNANCE M, WILKES BM, MOSSEY RT: Renal vascular disease causing end-stage renal disease: incidence. clinical correlates, and outcomes: a 20-year clinical experience. *Am J Kidney Dis* 24:622–629, 1994
24. NOVICK AC: Patient selection for intervention to preserve renal function in ischemic renal disease, in *Renal Vascular Disease*, edited by NOVICK AC, SCOBLE J, HAMILTON G, London, Saunders, 1996, p 323
25. SCHREIBER MJ, POHL MA, NOVICK AC: The natural history of atherosclerotic and fibrous renal artery disease. *Urol Clin North Am* 11:383–392, 1984
26. TOLLEFSON DFJ, ERNST CB: Natural history of atherosclerotic renal arterial disease associated with aortic disease. *J Vasc Surg* 14:327–331, 1991
27. STRANDNESS DE: Natural history of renal artery stenosis. *Am J Kidney Dis* 24:630–635, 1994
28. GUZMAN RP, ZEIRLER RE, ISAACSON JA, BERGELIN RO, STRANDNESS DE: Renal atrophy and arterial stenosis: a prospective study with duplex ultrasound. *Hypertension* 23:346–350, 1994
29. NOVICK AC: Management of renovascular disease: a surgical perspective. *Circulation* 83(Suppl I):I167–I171, 1991
30. REIDY RF, RITTER JM: Angioplasty in atheromatous renovascular disease (*editorial*). *Clin Radiol* 42:299–301, 1990
31. BLANKENHORN DH: Can atherosclerotic lesions regress? Angiographic evidence in humans. *Am J Cardiol* 65:41F–43F, 1990
32. WEBSTER J, SCOTTISH, NEWCASTLE RENOVASCULAR COLLABORATIVE GROUP: Prospective randomized trial of interventional (angioplasty) versus medical therapy in hypertensive patients with atheromatous renal artery stenosis. *Am J Hypertens* 8:38A, 1995
33. POHL MA, HORNER C, GOORMASTIC M, NOVICK A: Does renal revascularization preserve renal function in patients with atherosclerotic renal artery stenosis? An ongoing prospective study. *J Am Soc Nephrol* 2:242, 1991
34. SCOBLE JE, HAMILTON G: Atherosclerotic renovascular disease: remediable cause of renal failure in the elderly. *Br Med J* 300:1670–1671, 1990
35. KAYLOR WM, NOVICK AC, ZIEGELBAUM M, VIDT DG: Reversal of end stage renal failure with surgical revascularization in patients with atherosclerotic renal artery occlusion. *J Urol* 141:486–488, 1989
36. HANSEN KJ, THOMASON R, CRAVEN TE, FULLER SB, KEITH DR, APPEL RG, DEAN RH: Surgical management of dialysis-dependent ischemic nephropathy. *J Vasc Surg* 21:197–209, 1995
37. TEXTOR SC: Renovascular hypertension. *Endocrinol Metab Clin North Am* 23:235–253, 1994
38. MANN JFE: The diagnosis of renovascular hypertension: state of the art 1995. *Nephrol Dial Transplant* 10:1285–1286, 1995
39. TEXTOR SC: Renovascular hypertension. *Curr Opin Nephrol Hypertens* 2:775–783, 1993
40. SIGMON DH, BEIERWALTES WH: Renal nitric oxide and angiotensin II interaction in renovascular hypertension. *Hypertension* 22:237–242, 1993
41. TEXTOR SC, SMITH-POWELL L: Pathophysiology of renal failure in

ischemic renal disease, in *Renal Vascular Disease*, edited by NOVICK AC, SCOBLE J, HAMILTON G, London, Saunders, 1996, p 289
42. MOLITORIS BA: The potential role of ischemia in renal disease progression. *Kidney Int* 41(Suppl):S21–S25, 1992
43. TRUONG LD, FARHOOD A, TASBY J, GILLUM D: Experimental chronic renal ischemia: morphologic and immunologic studies. *Kidney Int* 41:1676–1689, 1992
44. SHANLEY PF: The pathology of chronic renal ischemia. *Semin Nephrol* 16:21–32, 1996
45. NIELSEN K, REHLING M, HENRIKSEN JH: Renal vein oxygen saturation in renal artery stenosis. *Clin Physiol* 12:179–184, 1992
46. TEXTOR SC: Pathophysiology of renal failure in ischemic nephropathy. *Am J Kidney Dis* 24:642–651, 1994
47. SOS TA: Angioplasty for the treatment of azotemia and renovascular hypertension in atherosclerotic renal artery disease. *Circulation* 83(Suppl I):I162–I166, 1991
48. NOVICK AC: Atherosclerotic ischemic nephropathy. *Urol Clin North Am* 21:195–200, 1994
49. BONELLI FS, MCKUSICK MA, TEXTOR SC, KOS PB, STANSON AW, JOHNSON CM, SHEEDY PF, WELCH TJ, SCHIRGER A: Renal artery angioplasty: technical results and clinical outcome in 320 patients. *Mayo Clinic Proc* 70:1041–1052, 1995
50. MACKAY A, BOYLE P, BROWN JJ, CUMMING AMM, FORREST H, GRAHAM AG, LEVER AF, ROBERTSON IS, SEMPLE PF: The decision on surgery in renal artery stenosis. *Q J Med* 51:363–381, 1983
51. VAUGHAN ED: Nephrology Forum: Renovascular hypertension. *Kidney Int* 27:811–827, 1985
52. LUSCHER TF, GREMINGER P, KUHLMANN U, STIEGENTHALER W, LARGIADER F, VETTER W: Renal venous renin determinations in renovascular hypertension. *Nephron* 44:17–24, 1986
53. LYONS DF, STERECK WF, KEM DC, BROWN RD, GALLOWAY DC, WILLIAMS GR, CHRYSANT SG, DANISA K, CAROLLO M: Captopril stimulation of differential renins in renovascular hypertension. *Hypertension* 5:615–622, 1983
54. GRIM CE, WEINBERGER MH: Diagnosis of renovascular hypertension: the case for renin assays, in *Controversies in Nephrology and Hypertension*, edited by NARINS RG, New York, Churchill Livingstone, 1984, p 109
55. ROUBIDOUX MA, DUNNICK NR, KLOTMAN PE, NEWMAN GE, COHAN RH, KADIR S, SVETKEY LP: Renal vein renins: inability to predict response to revascularization in patients with hypertension. *Radiology* 178:819–822, 1991
56. RAMSAY LE, WALLER PC: Blood pressure response to percutaneous transluminal angioplasty for renovascular hypertension: an overview of published series. *Br Med J* 300:569–572, 1990
57. ENGLUND R, BROWN MA: Renal angioplasty for renovascular disease: a reappraisal. *J Cardiovasc Surg* 32:76–80, 1991
58. CANZANELLO VJ, MILLAN VG, SPIEGEL JE, PONCE SP, KOPELMAN RI, MADIAS NE: Percutaneous transluminal renal angioplasty in management of atherosclerotic renovascular hypertension: results in 100 patients. *Hypertension* 13:163–172, 1989
59. BELL GM, REID J, BUIST TAS: Percutaneous transluminal angioplasty improves blood pressure and renal function in renovascular hypertension. *Q J Med* 63:393–403, 1987
60. MERCIER C, PIQUET P, ALIMI Y, TOURNIGAND P, ALBRAND J: Occlusive disease of the renal arteries and chronic renal failure: the limits of reconstructive surgery. *Ann Vasc Surg* 2:166–170, 1990
61. CHAIKOF EL, SMITH RB, SALAM AA, DODSON TF, LUMSDEN AB, KOSINSKI AS, COYLE KA, ALLEN RC: Ischemic nephropathy and concomitant aortic disease: a ten-year experience. *J Vasc Surg* 19:135–146, 1994
62. LAMAWANSA MD, BELL R, HOUSE AK: Short-term and long-term outcome following renovascular reconstruction. *Cardiovasc Surg* 3:50–55, 1995
63. THADHANI RI, CAMARGO CA, XAVIER RJ, FANG LST, BAZARI H: Atheroembolic renal failure after invasive procedures: Natural history based on 52 histologically proven cases. *Medicine* 74:350–358, 1995
64. TEXTOR SC, HALLETT JW, KOS PB, SCHNEIDER CL, NICPON G, SCHRIGER A: Outcomes and risks of renal revascularization in azotemic atherosclerotic patients. *J Am Soc Nephrol* 6:405, 1995
65. ZUCCALA A, ZUCCHELLI P: Atherosclerotic renal artery stenosis—when is intervention by PTA or surgery justified? *Nephrol Dial Transplant* 10:585–600, 1995
66. TEXTOR SC: Atherosclerotic renovascular disease as a cause of end-stage renal disease: cost considerations. *Blood Purif* 14:305–314, 1996
67. MESSINA LM, ZELENOCK GB, YAO KA, STANLEY JC: Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. *J Vasc Surg* 15:73–82, 1992
68. ZIERLER RE, BERGELIN RO, DAVIDSON RC, CANTWELL-GAB K, POLISSAR NL, STRANDNESS DE: A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. *Am J Hypertens* 9:1055–1061, 1996
69. CROWLEY JJ, CONLON PJ, SANTOS RM, KRUSE KR, ATHIRAKUL K, PHILLIPS HR, STACK RS: Incidence and progression of renal artery atherosclerosis in patients undergoing cardiac catheterization. *Circulation* 94:I299, 1996
70. BLUM U, KRUMME B, FLUEGEL P, GABELMANN A, LEHNERT T, BUITRAGO-TELLEZ C, SCHOLLMEYER P, LANGER M: Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty. *N Engl J Med* 336:459–465, 1997
71. JACKSON B, MATTHEWS PG, MCGRATH BP, JOHNSTON CI: Angiotensin converting enzyme inhibition in renovascular hypertension: frequency of reversible renal failure. *Lancet* 1:225–226, 1984
72. JACKSON B, FRANZE L, SUMITHRAN E, JOHNSTON CI: Pharmacologic nephrectomy with chronic angiotensin converting enzyme inhibitor treatment in renovascular hypertension in the rat. *J Lab Clin Med* 115:21–27, 1990
73. LERMAN LO, TALER SJ, TEXTOR SC, SHEEDY PF, STANSON AW, ROMERO JC: Computed tomography-derived intrarenal blood flow in renovascular and essential hypertension. *Kidney Int* 49:846–854, 1996
74. WEIBULL H, BERGQVIST D, BERGENTZ SE, JONSSON K, HULTHEN L, MANHEM P: Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: a prospective randomized study. *J Vasc Surg* 18:841–850, 1993
75. STRANDNESS DE: Duplex ultrasound scanning, in *Renal Vascular Disease*, edited by NOVICK AC, SCOBLE J, HAMILTON G, London, Saunders, 1996, p 119
76. O'NEIL EA, HANSEN KJ, CANZANELLO VJ, PENNELL TC, DEAN RH: Prevalence of ischemic nephropathy in patients with renal insufficiency. *Am Surg* 58:485–490, 1992
77. WELCH HG, ET AL: Estimating treatment benefits for the elderly: the effect of competing risks. *Ann Intern Med* 124:577, 1996
78. ROMERO JC, FELDSTEIN AE, RODRIGUEZ-PORCEL MG, CASES-AMENOS A: New insights into the pathophysiology of renovascular hypertension. *Mayo Clin Proc* 72:251–260, 1997
79. FARIA FA, SALGADO MC: Facilitation of noradrenergic transmission by angiotensin in hypertensive rats. *Hypertension* 19(Suppl 2):II30–II35, 1992
80. BLANKENHORN DH: Regression of atherosclerosis: what does it mean? *Am J Med* 90(2A):42S–47S, 1991
81. ZWEIER JL, KUPPUSAMY P, LUTTY GA: Measurement of endothelial cell free radical generation: evidence for a central mechanism of free radical injury in post-ischemic tissues. *Proc Natl Acad Sci USA* 85:4046–4999, 1988
82. MICHEL JB, DUSSAULE JC, CHONDAT L, ANZAN C, NOCHY D, CORVOL P, MENARD J: Effects of antihypertensive therapy in one-clip, two-kidney hypertension in rats. *Kidney Int* 29:1011–1020, 1986
83. VENIANT M, HENDES D, CLOZEL JP, BRUNEVAL P, MENARD J: Calcium blockade versus ACE inhibition in clipped and unclipped kidneys of 2K–1C rats. *Kidney Int* 46:421–429, 1994
84. TEXTOR SC, SMITH-POWELL L: Post-stenotic arterial pressure, renal haemodynamics and sodium excretion during graded pressure reduction in conscious rats with one- and two-kidney coarctation hypertension. *J Hypertens* 6:311–319, 1988
85. GRONE HJ, HELMCHEN U: Impairment and recovery of the clipped kidney in two kidney, one clip hypertensive rats during and after antihypertensive therapy. *Lab Invest* 54:645–655, 1986
86. RIMMER JM, PLANTE DA, MADIAS NE: Therapeutic decision making in renal vascular hypertension, in *Renal Vascular Disease*, edited by NOVICK AC, SCOBLE J, HAMILTON G, London, Saunders, 1997, p 245
87. COHEN EP, ELLIOTT WC JR: The role of ischemia in acquired cystic kidney disease. *Am J Kidney Dis* 15:55–60, 1990